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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/816,591
Filing Date: April 01, 2004
Appellant(s): FUERTES-LOPEZ ET AL.

Ursula B. Day

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/9/10 appealing from the Office action mailed 4/1/09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claim 24.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,451,593 Wittig et al. 9-2002

Gurunathan et al. (1997) J. Exp. Med., Vol. 186(7), 1137-1147

Makkerh et al. (1996) Current Biology, Vol. 6 (8), 1025-1027.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 24 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Gurunathan et al. (1997) J. Exp. Med., Vol. 186(7), 1137-1147, in view of U.S. Patent No. 6,451,593 (2002),

hereafter referred to as Wittig et al., and Makkerh et al. (1996) Current Biology, Vol. 6 (8), 1025-1027.

Gurunathan et al. teaches a DNA expression construct encoding the p36 LACK antigen from *Leishmania major* operatively linked to the CMV promoter and a polyA sequence and the use of the construct as a vaccine to generate protective immunity against *Leishmania major* in a mammal (Gurunathan et al., pages 1137-1139).

Gurunathan et al. differs from the instant invention in that the DNA expression construct taught by Gurunathan et al. is a plasmid DNA, and in that the DNA is not covalently linked to an oligopeptide such as PKKKRKV. Wittig et al. supplements Gurunathan et al. by teaching dumbbell shaped DNA expression constructs comprising covalently closed linear DNA that contains only a coding sequence operably linked to a promoter and polyA termination sequence, where the linear ends are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to a peptide which directs transport of the construct across a cell's endosome or into the nucleus (Wittig et al., claims 1-11, and columns 5-8)). In particular, Wittig et al. specifically teaches the use of the nuclear localization sequence (NLS) from SV40, a sequence which inherently comprises PKKKRKV (Wittig et al., column 5). Wittig et al. also teaches as a preferred embodiment a vaccine comprising this construct for treating infectious diseases (Wittig et al., columns 1 and 8). Wittig et al. further provides motivation for using a dumbbell DNA expression construct linked to a peptide over a plasmid DNA expression construct. Wittig et al. teaches that because the dumbbell construct consists only of a promoter-gene-terminator sequence, these constructs have none of the disadvantages of plasmid constructs, including their size, which inhibits fast transport into the cell's nucleus, and the presence of

unwanted background sequences, including bacterial sequences, which can lead to unintended immune responses (Wittig et al., columns 2-3, bridging paragraph).

While Wittig et al. does teach to use an oligopeptide covalently attached to the DNA construct for nuclear transport, and specifically teaches the use of the NLS from SV40, Wittig et al. does not specifically teach that the peptide consists of PKKKRKV. However, at the time of filing, the exact nuclear localization sequence (NLS) of SV40 was known. Makkerh et al. teaches that the sequence consisting of PKKKRKV is the defined nuclear localization sequence of SV40, which can be used to target heterologous molecules to the nucleus (Makkerh et al., page 1025, and Table I, page 1027).

Therefore, based on the advantages to using dumbbell DNA expression constructs over plasmid constructs for immunization as taught by Wittig et al., the motivation to covalently attach a peptide such as an NLS from SV40 to a dumbbell DNA expression construct also provided by Wittig et al., and the known sequence of the NLS peptide from SV40 as provided by Makkerh et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to make a dumbbell DNA construct according to the teachings of Wittig et al. which encodes p36 LACK as taught by Gurunathan et al., and which is further linked to the defined NLS peptide PKKKRKV as taught by Makkerh et al. Further, based on the substantial guidance for making dumbbell constructs provided by Wittig et al., the skilled artisan would have had a reasonable expectation of success in making a dumbbell DNA expression construct capable of being used as a vaccine against *Leishmania major* which encodes the p36 LACK antigen and which is covalently linked to a peptide such as the NLS PKKKRKV peptide from SV40.

(10) Response to Arguments

The appellant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues in section (a) that there is no motivation found in Gurunathan for the skilled artisan to modify the teachings of Gurunathan with Wittig and Makkerh. Specifically, the appellant argues that the instant specification identifies several drawbacks to using plasmids such that the skilled artisan would not start out with the teachings of Gurunathan, and that Gurunathan does not provide any motivation to modify their invention to reach the invention of claim 24. The appellant also states that motivation to combine was not abolished by the Supreme Court, citing *Ex parte Whalen*.

In response, it is first noted that the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). However, there is clearly no requirement that the primary reference, Gurunathan et al., provide this motivation. In this case, Wittig et al., the secondary reference, provides specific motivation to use a dumbbell DNA construct, also known as a MIDGE vector, over plasmid vectors by teachings several disadvantages of plasmid vectors which are overcome by the use of MIDGE vectors. Gurunathan et al. was cited as the primary reference as it is the

closest prior art to the instant claim. Gurunathan et al. is clearly analogous art as it teaches a DNA expression construct encoding the p36 LACK antigen from *Leishmania major* operatively linked to the CMV promoter and a polyA sequence and the use of the construct as a vaccine to generate protective immunity against *Leishmania major* in a mammal (Gurunathan et al., pages 1137-1139). The rejection of record further acknowledged that Gurunathan et al. differs from the instant invention in that the DNA expression construct is a plasmid not a MIDGE and in that the DNA is not covalently linked to an oligopeptide such as PKKKRKV. However, Wittig et al. was cited to supplement Gurunathan et al. by teaching dumbbell shaped DNA expression constructs (aka MIDGE vectors) comprising covalently closed linear DNA that contains only a coding sequence operably linked to a promoter and polyA termination sequence where the linear ends are linked by short single stranded loops of DNA, and wherein the construct is further covalently linked to a peptide which directs transport of the construct across a cell's endosome or into the nucleus (Wittig et al., claims 1-11, and columns 5-8)). Wittig et al. also teaches a vaccine comprising this construct for treating infectious diseases (Wittig et al., columns 1 and 8). Wittig et al. was further cited for providing motivation for using a dumbbell DNA expression construct linked to a peptide over a plasmid DNA expression construct. Wittig et al. teaches that because the dumbbell construct consists only of a promoter-gene-terminator sequence, these constructs have none of the disadvantages of plasmid constructs, which include their size, which inhibits fast transport into the cell's nucleus, and the presence of unwanted background sequences, including bacterial sequences, which can lead to unintended immune responses (Wittig et al., columns 2-3, bridging paragraph). Thus, Wittig et al. specifically teaches that the problems with plasmids alluded to by appellants were known in the art and specifically teaches that the use of a

dumbbell construct (MIDGE) overcomes these problems. Since Wittig et al. provides clear teachings and motivation to modify the methods of Gurunathan et al., the skilled artisan at the time of filing would have had ample motivation to make a MIDGE vector encoding p36 LACK as claimed.

The appellant further argues in section (a) that Gurunathan et al. teaches the importance of IL-12 and IFN-gamma in generating effective immune responses to the LACK antigen and that Gurunathan et al. suggests that immunostimulatory bacterial sequences present in the plasmid encoding LACK contribute to the generation of IL-12 and IFN-gamma. Applicant continues by arguing that since Gurunathan et al. teaches the contribution of bacterial sequences present in the plasmid that the skilled artisan would not have been motivated to use a MIDGE vector which lacks the majority of these sequences to express p36 LACK.

In response, it is first noted that the sole claim under examination is a product claim, not a method claim. While the product is identified as a "vaccine for vaccinating a living being against infection by leishmania", the patentability of the product depends on the claimed structure of the product and not on its intended use as a vaccine for vaccinating. However, it is also noted that while Gurunathan et al. comments that bacterial immunostimulatory sequence present in the plasmid may contribute to the observed immune response to LACK, the actual data presented by Gurunathan et al. shows that whereas the control plasmid, which theoretically contains the immunostimulatory sequences, does not appear to induce any detectable amount of IFN-gamma when administered *in vivo*, the plasmid encoding LACK DNA induced significant amounts of IFN-gamma (see Figure 7, the control DNA lane, and Figure 5). In fact, the control DNA appears to stimulate IL-4 production, not IFN-gamma production in these experiments (see

Figure 5B). Since IL-4 is detrimental to the induction of therapeutic immune responses in Leishmania, the skilled artisan reading Gurunathan et al. could only conclude that the LACK DNA itself contributes to the generation of IFN-gamma and results in the generation of a therapeutic immune response in vaccinated mice challenged with *L. major*. Furthermore, as noted above and in the rejection of record, Wittig et al. supplements Gurunathan et al. by teaching that MIDGE constructs encoding antigens are capable of generating therapeutic immune responses against infectious diseases and have several advantages over complete plasmid vectors which have been discussed in detail above and in previous office actions. As such, the skilled artisan, when reading the teachings of Gurunathan et al. as a whole, in view of Wittig et al. would in fact have been motivated to make a MIDGE construct encoding p36 LACK. In addition, based on the data in Gurunathan et al. discussed above, and the teachings of Wittig et al., the skilled artisan at the time of filing would have had a reasonable expectation that a MIDGE construct encoding p36 LACK could be used as a vaccine. The appellant is reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

The appellant argues in section (b) that the examiner has misunderstood the science of Gurunathan et al.. The appellant states that Gurunathan et al. demonstrates that the immunostimulatory sequences in the bacterial plasmid are essential to the generation of the therapeutic immune response since administration of p36 LACK protein does not generate significant amounts of IFN-gamma, or have a significant effect on foot pad swelling.

In response, it is not agreed that there has been any misunderstanding of the science of Gurunathan et al. Appellant's argument that the failure of LACK protein by itself to generate an effective immune response shows that it is the bacterial sequences in the plasmid and not the LACK antigen which stimulates an immune response resulting in IFN-gamma and IL-12 is not persuasive since the administration of protein antigen generates substantially different immune responses than the administration of nucleic acid encoding a antigen due to access of the different forms of the antigen to different antigen presentation pathways which stimulate different types of immune cells. It was well known at the time of filing that the delivery of DNA encoding an antigen stimulates a Th1 type response and allows for intracellular expression and processing of the encoded antigen for presentation on MHC class I which stimulates a CD8+ T cells as shown and discussed by Gurunathan et al. in Figure 9, page 1144, and on page 1137. Th1 type helper T cells and CD8+ T cells can both secrete IFN-gamma. Protein antigen does not typically access the class I pathway and thus generates a materially different immune response. Thus, the fact that p36 LACK protein administration did not stimulate IFN-gamma production or significantly affect foot pad swelling is not indicative of the immune stimulating potential of nucleic acid encoding p36 LACK, and does not teach or suggest that the stimulation of IFN-gamma requires the presence of bacterial DNA sequences in the plasmid. However, it is also noted, for the record, that MIDGE constructs comprising a promoter, nucleic acid encoding p36LACK, and a polyadenylation sequence, are produced in bacteria and may therefore also contain unmethylated CpG sequences which are immunostimulatory. Finally, while Gurunathan et al. suggests that the bacterial immunostimulatory sequences can improve the therapeutic immune response, there is nothing in Gurunathan et al. which suggests that a minimal bacterially

derived expression cassette, such as a MIDGE vector taught by Wittig et al., would be incapable of stimulating IFN-gamma, or IL-12. Further, Wittig et al. has been cited for specifically teaching that MIDGE vectors encoding an antigen have several advantages over plasmid vectors and can be used as vaccine for therapeutic disease, and nothing in Gurunathan et al. disputes the teachings of Wittig et al. As such, since the rejection of record is based on the combined teachings of Gurunathan et al. in view of Wittig et al. and Makkerh et al., it is maintained that the skilled artisan reading all three references in their entirety would have found both motivation to make a product as claimed and a reasonable expectation that the product would have been capable of being used as a vaccine for leishmania.

In section (c), the appellant argues that the teachings of Gurunathan et al. have not been considered in their entirety because the examiner has focused on the results using LACK DNA and not the results using LACK protein.

In response, the office has fully considered all the teachings of Gurunathan, including results using LACK protein, see above, and has not found that Gurunathan et al. teaches away from or precludes the skilled examiner from following the suggestion of Wittig et al. to remove the extraneous bacterial sequences from the expression vector.

In section (d), the appellant argues that the use of PKKKRKV as the NLS is not obvious from the teachings of Wittig et al. because Wittig et al. discloses the use of three different signal peptides, one of which is the SV40 NLS, and according to applicant, there would have been uncertainty as to which of the three would be successful when covalently attached to a MIDGE construct in nuclear localization. The applicant also states that Wittig et al. does not specifically teach SEQ ID NO:3 and that it is irrelevant that this sequence was already known, as taught by

Makkerh, because the crucial selective step is to decide which of the three variants proposed by Wittig would be successful.

In response, the appellant concedes in their remarks on page 11 of the instant Appeal Brief that the NLS of SV40, and specifically SEQ ID NO:3, was well known at the time of filing, and had been used successfully in the prior art for nuclear localization. There is no evidence of record to suggest that the skilled artisan would have considered it unpredictable to use any known NLS covalently attached to a MIDGE as taught by Wittig et al. for nuclear localization, or that the skilled artisan would have considered it unpredictable that the well known SV40 NLS would be functional for nuclear localization when covalently attached to a MIDGE. As such, since the SV40 NLS RKKKRKV was well known as a nuclear localization signal sequence, see Makkerh et al., and Wittig et al. clearly teaches the covalent attachment of an NLS such as the SV40 NLS to a MIDGE construct, there is clear motivation to make such as construct and a reasonable expectation of success that the SV40 NLS, when attached to the MIDGE construct, would be functional.

In section (e), the appellant argues that the examiner has not fully considered the Declaratory evidence provided by the Timon-Jimenez Declaration or the supporting references. In response, it is first noted that of the four references discussed in appellant's remarks accompanying the Declaration, only one reference, the Lopez-Fuertes et al. reference, was actually provided to the examiner for consideration before the mailing of the Final office action on 4/1/09. Neither Kalderon reference, nor the Zanta reference were provided for the examiner's consideration with the response filed on 4/3/08, or the supplemental responses of 4/9/08 and 4/9/08. These three references were provided for the first time with the after-final request for

reconsideration filed on 5/28/09. However, the advisory action mailed on 7/10/09 clearly stated that these references were not made of record or considered by the examiner since the applicant had not explained why this evidence is necessary and why it was not submitted earlier as required by 37 CFR 1.116(e). Thus, although the appellant has listed these references, Kalderon, Kalderon, and Zanta, as evidence relied upon in the evidence appendix of the instant Appeal Brief, and provided arguments based on the teachings of these references, the references are not part of the record and have not been considered by the examiner. Therefore, it is submitted that the examiner did in fact consider all supporting references which were properly made of record during prosecution of this application.

The appellant further argues in section (e) that the Declaration previously provided with the response of 5/9/08 is both commensurate in scope with the instant claim and further provides evidence of unexpected results. The Declaration provides the results of experiments which utilize a MIDGE-NLS where the sequence of the NLS is PKKKRKVEDPYC (Lopez-Fuertes et al., page 248, column 2). The instant claims are drawn to an NLS which consists of the sequence PKKKRKV. According to applicant, the functional unit of the NLS sequence used in Lopez-Fuertes et al. is functionally equivalent to SEQ ID NO:3 because the additional short amino acid sequence EDPYC added to PKKKRKV by Lopez-Fuertes et al. was known in the prior art and is nonfunctional. However, despite applicant's argument, there is no evidence of record to suggest that the longer oligopeptide in Lopes-Fuertes et al. is identical in function to the smaller PKKKRKV sequence. Thus, it is not agreed that the evidence provided in Lopez-Fuertes et al. is commensurate in scope to the instant claim.

In regards to the argument that the Declaration demonstrates unexpected results, the appellant is reminded that any evidence of unexpected results must be commensurate in scope with the claimed invention. MPEP 716.02 (d). As discussed above, it is not agreed that the evidence provided in Lopez-Fuertes et al. is commensurate in scope to the instant claim. Second, it has been noted that a greater, or greater than additive, effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) and MPEP 716.02 (a). In the instant case, the declaration states that priming and boosting with NLS-modified MIDGE encoding p36 was superior to the best vaccination protocols available which used priming with plasmid DNA encoding and boosting with rVV (see page 3 of the Timon-Jimenez Declaration). The declaration refers to data set forth in the Lopez-Fuertes et al. post-filing publication of which the inventors were authors. However, while the Lopez-Fuertes et al. publication shows that priming and boosting with MIDGE-p36-NLS results in decreased lesion size compared to priming and boosting with MIDGE-p36 (no NLS), the authors of Lopez-Fuertes et al., including the instant inventors, concluded that prime/boost with MIDGE-p36-NLS induces "at least as good" protection as with prime/boost of plasmid-p36/vaccinia-p36 (Lopez-Fuertes et al., page 252, column 1). In particular, please note that on page 252, column 2, of Lopez-Fuertes et al. it is clearly stated in regards to the results depicted in Table 2 that, "[t]he difference in lesion size between MIDGE-p36-NLS/ MIDGE-p36-NLS and pMOK-p36/rVVp36 immunized animals was not significant". Also on page 252, column 2, the authors state, "[a]s shown in Fig. 2A, the extend of protection triggered by the protocol based on priming/boosting with MIDGE-p36-NLS was similar to that induced by priming/boosting with pMOK-p36 and

rVVp36, showing not statistically significant differences between both groups". Thus, the actual results and the clear statements in the Lopez-Fuertes et al. publication that differences seen in Table 2 and Figure 2 between the MIDGE-p36-NLS/ MIDGE-p36-NLS and pMOK-p36/rVVp36 immunized animals were not significantly different do not support appellant's contention of unexpected results.

The appellant further argues that the observed comparable response still represents unexpected results because the generation of protective immunity is a complex process such that success with a plasmid vector encoding p36 LACK would not be predictive of success with MIDGE-p36LACK-NLS. In response, this is not agreed for reasons of record. First, the claim is a product claim, not a method of generating protective immunity. The appellant is reminded that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Second, as discussed in detail above, Wittig et al. clearly teaches that MIDGE constructs encoding antigens are capable of generating therapeutic immune responses and have several advantages over complete plasmid vectors. It is also noted that the state of the art for generating immune responses against pathogenic antigens at the time of filing included teachings that numerous expression vectors were capable of expressing pathogenic antigens and generating antigen specific immune responses, including plasmids, adenoviral vectors, retroviral vectors, vaccinia virus vectors, herpes virus vectors etc., such that the skilled artisan would indeed have had a reasonable expectation of success that a MIDGE-p36LACK-NLS as taught by the combined teachings of Gurunathan et al. in view of Wittig et al. and Makkerh et al. could be

used to generate immune responses *in vivo*. Thus, for reasons of record as discussed in detail above, the declaratory evidence of record does not establish unexpected results for the claimed product.

In conclusion, since Gurunathan et al. teaches plasmid vectors encoding p36 LACK for use in vaccinating a living subject, and Wittig et al. specifically teaches that the problems with plasmids alluded to by applicants were known in the art, and specifically teaches that the use of a dumbbell construct (MIDGE) overcomes these problems, Wittig et al. as supplemented by Makkerh et al. provides clear teachings and motivation to modify the methods of Gurunathan et al. to arrive at the instant product as claimed. As such, it is not agreed that impermissible hindsight was used to construct the instant rejection. Therefore, the rejection of record stands.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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